

RELEVANCE OF NICOTINE-DERIVED N-NITROSAMINES  
IN TOBACCO CARCINOGENESIS

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Human exposure to N-nitroso compounds is widespread. Chewing tobacco, snuff, and tobacco smoke contain tobacco-specific N-nitrosamines (TSNA) far in excess of concentrations of nitrosamines reported in other consumer products. TSNA are formed from nicotine and the minor Nicotiana alkaloids during tobacco processing and smoking. They induce benign and malignant tumors of the upper aerodigestive tract, lung, liver and/or exocrine pancreas in mice, rats and hamsters. The epidemiological studies on snuff dippers strongly support the contention that TSNA contribute significantly to the increased cancer risk of tobacco consumers. The known carcinogens in snuff are certain aldehydes, polonium-210, polynuclear aromatic hydrocarbons, and TSNA which are the major carcinogens in snuff. A mixture of N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), swabbed daily on the oral tissue of rats (total doses: 1.6 mM/kg) induced a significant incidence of oral tumors. The lifetime exposure of a snuff dipper to NNN and NNK amounts to approximately 0.4 mmol/kg. In addition, endogenous formation of TSNA during tobacco usage is likely.

Biochemical studies strongly support the contention that TSNA make a significant contribution to the carcinogenic risk of tobacco chewers and smokers. NNN and NNK require metabolic conversion to active species which react with cellular components including DNA. In human tissue explants of oral cavity, lung and liver, NNN and NNK are metabolically activated in the same way as in mice, rats and hamsters. In snuff dippers and smokers, TSNA form also globin adducts, which are studied as markers of exposure to NNN and NNK. The concentration of the TSNA adducts in the blood of snuff dippers exceeds that expected from the TSNA content of the consumed tobacco. This finding supports the concept that TSNA are also formed endogenously in tobacco consumers. Compared to nonsmokers, cigarette smokers have a higher potential for endogenous N-nitrosamine formation as is reflected in their higher urinary excretion of N-nitrosoproline and N-nitrosothiopropine.

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